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14. ABSTRACT

Following a traumatic orthopaedic injury, the affected muscle tissue is susceptible to a disease known as heterotopic ossification (HO), which is characterized by the formation of bone in the soft tissue. This disease is especially common in soldiers that have sustained severe injuries during military operations. The current studies are directed at identifying early- appearing biomarkers in the animal model that predict the occurrence of HO in the animal model and may well similarly predict the development of HO in the human condition.

Patients exhibiting biomarkers predictive of exuberant HO formation can then be identified before the disease process begins and treated prophylactically.

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Introduction:

Heterotopic ossification (HO), characterized by the pathologic formation of mature bone in the soft tissues,is a frequent complication following high energy orthopaedic trauma. HO is prevalent in patients with severe extremity war-time wounds; specifically, its incidence is reported as high as 57% in patients that sustain a poly trauma blast injury [1]. Complications related to HO in residual limbs following blast amputation include pain, overlying skin and muscle breakdown, poor fitting and functioning of prosthetic limbs, reoperation for amputation revision, and impaired limb function that delays or limits rehabilitation [2-6]. Current treatments to prevent HO are limited to mitigation rather than prevention. Furthermore, removal of heterotopic bone after it has formed can be difficult; this frequently requires resection of substantial amounts of soft tissue and risks injury to adjacent neurovascular structures that are often intimately associated with the ectopic bone. It is preferable to address the issue of HO before it begins. Prevention of HO in residual limbs is needed to offer amputation survivors the best possible quality of life and return to function. We have developed a blast amputation animal model and validated that it replicates the human condition with respect to formation of HO. The current studies are directed at identifying early-appearing biomarkers in the animal model that predict the occurrence of HO in the animal model and may well similarly predict the development of HO in the human condition. Patients exhibiting biomarkers predictive of exuberant HO formation can then be identified before the disease process begins and treated prophylactically.

Keywords: Heterotopic ossification, blast injury, amputation, bone formation, animal model, rat model, gene expression, protein expression, biomarkers

Overall Project Summary:

Current objectives: We have completed all thirty hind-limb blast amputation procedures indicated for Task 1 of Specific Aim 1. These animals are now being survived out 24 weeks and followed with serial x-rays. Fifteen of the animals underwent bilateral muscle biopsy procedure at two weeks and fifteen underwent biopsy procedure at four weeks, as per protocol. The biopsy specimens have been received initially processed at the Nesti lab. They will be analyzed for both gene- and protein-level biomarkers and will be compared to gene expression signatures in existing human tissue samples known to be characteristic for the formation of heterotopic ossification.

Results: Biomarker analysis, from 24 h, 72 h and two- and four-week biopsy specimens to identify molecular predictors of HO, is currently underway on the first group of sixty biopsy specimens. There are no results available at this time.

Progress and Accomplishments: Facilities have been established for conduct of the blast model at MUSC and all necessary institutional and state regulatory approvals have been obtained. We have completed all hind-limb blast amputation procedures on 30 animals, with 100% animal survival, as well as related scheduled biopsies included in Task 1 of Specific Aim 1. There has been a delay in the distribution

of funds for the Nesti lab. This has resulted in an unexpected delay in protein and gene expression profiling as well as human tissue comparison. This delayed has occurred concurrently with a lab move from NIH to USUHS. Overall, we expect these delays to contribute to a 12-18mo delay in project completion.

Since the project inception, combat OPTEMPO has changed and there are few if any casualties passing through LRMC. This will make it difficult if not impossible to obtain the appropriate number of specimens at that site. For this reason, we have changed our research plan to expand the number of human specimens to be evaluated from our repository in the Nesti lab and we will submit a revised SOW and budget to accommodate and justify these changes.

Key Research Accomplishments: Nothing to report

Conclusion: Research is continuing with an expected 12-18mo delay that reflects the delay in funds distribution for the Nesti lab and the lab move from NIH to USUHS. A revised SOW and budget will be submitted to accommodate the change associated with the loss of LRMC as a study site.

Publications, Abstracts and Presentations: Nothing to report

Inventions, Patents and licenses: Nothing to report

Reportable Outcomes: Nothing to report

Other Achievements: Nothing to report

References:

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Appendices: None